Food and Drug Administration
Center for Biologics Evaluation and Research
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To: Administrative File: STN 125597/0

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From: Christine Harman, Chemist, CMC/Facility Reviewer/Inspector, CBER/OCBQ/DMPQ/BI

Through: Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/BI

Applicant: PaxVax, Bermuda Ltd.

Product: Cholera Vaccine, Live Oral (Powder for suspension)
Trade name: Vaxchora®

Indication: For active immunization of adults against disease caused by *V. cholera* serogroup O1

Subject: Primary Review: Original BLA for Vaxchora covering the review of areas relating to DMPQ aspects

Due Date: June 15, 2015

RECOMMENDATION

At this time, there is no recommendation as there are outstanding information requests and inspections yet to be completed. Please refer to sections: "X. Information Requests" and "XI. Overall List of Inspection Follow-ups" of this memo for a listing of all outstanding information to be covered in the addendum review memo.

EXECUTIVE SUMMARY

This BLA from PaxVax was received by the Agency on October 16, 2015 as an electronic submission in eCTD format (0000), in addition, two amendments were received which include amendment 1 on October 19, 2015 (updated facilities table) and amendment 2 October 28, 2015 (correction to the Establishment section of 356h form) both of which are in eCTD format. This BLA was granted priority review status; therefore, is reviewed under the 6 month review timeframe. This review covers the aspects of the BLA submission that are under the purview of DMPQ as per responsibilities outlined in "SOPP 8401.4: Review Responsibilities for CMC Section of Biologic License Applications and Supplements". The review of other aspects of the

submission under purview of other offices/divisions as outlined in SOPP 8401.4 are deferred to the appropriate office/division. The sections of the BLA that were reviewed by DMPQ and that are summarized in this review include in the following sections of the BLA:

Module 1: Regional

1.1 Forms

- Form FDA 356h

1.2 Cover Letters

1.12 Other Correspondence

- 1.12.14 Environmental Analysis

Module 2: Common Technical Document Summaries

2.2 Introduction

2.3 Quality Summary

- 2.3.S Drug Substance [Substance-Manufacturer]
- 2.3.P Drug Product [Product-Dosage Form-Manufacturer]
- 2.3.A Appendices

Module 3: Quality

3.2.S PXVX0200-PaxVax

- 3.2.S.1 General Information
- 3.2.S.2. Manufacture
    - 3.2.S.2.1 Manufacturer(s)
    - 3.2.S.2.2 Description of Manufacturing process and Process Controls
    - 3.2.S.2.4 Controls of Critical Steps and Intermediates
    - 3.2.S.2.5 Process Validation
    - 3.2.S.2.6 Manufacturing Process Development
- 3.2.S.6 Container Closure

3.2.P Drug Product [Product-Dosage Form-Manufacturer]

- 3.2.P PXV0200 Powder for Oral Suspension-PaxVax
    - 3.2.P.1 General Information
    - 3.2.P.2 Pharmaceutical Development
    - 3.2.P.3 Manufacture
        - 3.2.P.3.1 Manufacturer (s)
        - 3.2.P.3.3 Description of Manufacturing process and process controls
        - 3.2.P.3.4 Control of Critical Steps and Intermediates
        - 3.2.P.3.5 Process Validation
    - 3.2.P.7 Container Closure
- 3.2.P Buffer Effervescent Granule- (b) (4)
    - 3.2.P.1 General Information
    - 3.2.P.2 Pharmaceutical Development
    - 3.2.P.3 Manufacture
        - 3.2.P.3.1 Manufacturer (s)
        - 3.2.P.3.3 Description of Manufacturing process and process controls
        - 3.2.P.3.4 Control of Critical Steps and Intermediates
        - 3.2.P.3.5 Process Validation
    - 3.2.P.7 Container Closure

3.2.A. Appendices*

- 3.2.A.1 (b) (4) - Powder for Oral Suspension Facilities and Equipment
- 3.2.A.1 (b) (4) - Facilities and Equipment

*Note: all documents provided in sections 3.2.A.1 (b) (4)/PaxVax Facilities and Equipment and 3.2.A.1 (b) (4) Facilities and Equipment are covered in this review.

BLA REVIEW NARRATIVE

I. **Description of product and proposed indication:** Vaxchora™ (Cholera Vaccine, Live, Oral) is a live attenuated bacterial vaccine containing the CVD 103-HgR vaccine strain Vibrio cholera serogroup O1, biotype classical, serotype Inaba. The vaccine drug product consists of a co-package of a single-dose, multilayer foil sachet containing vaccine powder and a separate single dose, multilayer foil sachet containing buffer powder. The vaccine is administered orally, thus requires reconstitution of the buffer and vaccine powders. The reconstitution procedure includes dissolution of the buffer powder in 100 mL of bottled water, followed by the addition of vaccine powder then mixing. Once reconstituted the vaccine is administered orally. The dosage strength is 4×10^8- 2×10^9 CFU/dose of recombinant live attenuated *V. cholera* vaccine strain CVD 103-HgR. The indication is proposed for active immunization of adults against disease caused by V. cholera serogroup O1 and is intended for use by individuals from non-cholera endemic areas who may be at risk of cholera infection i.e. through travels to such endemic/epidemic areas.

II. **Composition of the drug product and buffer drug product**: The composition for a single dose of vaccine includes viable and non-viable CVD 103-HgR bacteria, ascorbic acid, sucrose and lactose monohydrate as excipients. The buffer sachet includes sodium bicarbonate, ascorbic acid and lactose monohydrate. Reference the table below for details on ingredients, quantity and function of contents of vaccine sachet:

Final Drug Product Composition

Ingredient	Quantity	Function
Viable CVD 103-HgR	(b) (4)	Active ingredient
Non-Viable CVD 103-HgR	(b) (4)	Active ingredient
Hy-Case SF	(b) (4)	Media component
Ascorbic Acid	(b) (4)	Stabilizer (anti-oxidant)
Sucrose	(b) (4)	Stabilizer
Lactose monohydrate	(b) (4) g	Excipient

The above table assumes the following: Bulk Drug Substance CFU/g is: (b) (4)

III. **Overall Manufacturing Procedure and Facilities involved**: The manufacturing of the drug substance and drug product is performed at two facilities: (b) (4) and PaxVax (b) (4). The manufacturing of bulk buffer is performed at (b) (4). A brief description of the overall manufacturing operations performed at each of the facilities is briefly summarized as follows:

(b) (4) manufactures the Intermediate Bulk Drug Substance (IBDS). Manufacturing of the Intermediate Bulk Drug Substance (IBDS) begins with (b) (4) The IBDS is shipped to PaxVax for further manufacturing to DP. The specific details of the manufacturing operations performed at the (b) (4) facility are provided in section **3.2.S. Drug Substance Manufacturing** of this memo.

PaxVax: IBDS received from (b) (4) is further processed to produce BDS involving the following unit operations: Receipt and Storage of IBDS, Milling and Mixing of the

lyophilisate, Blending of milled BDS with lactose to BDS, and Filling of the DP into sachets. Pax Vax facility also performs the operations of the filling of bulk buffer product into foil sachets. The bulk buffer drug product is received from (b) (4), stored and then filled into sachets. The specific details of the manufacturing operations performed at Pax Vax, Inc. facility are provided in sections **3.2.S. Drug Substance Manufacturing, 3.2.P Drug Product Manufacturing,** and **3.2.P Buffer Drug Product Manufacturing- Effervescent Granule** of this memo.

(b) (4): Manufacturing of the bulk Buffer Drug Product is performed at (b) (4) and the filling of the bulk buffer drug product into sachets is performed at Pax Vax, Inc. facility in (b) (4). The bulk buffer manufacturing starts with the (b) (4) The material is then packaged, stored and then shipped to Pax Vax. The specific details of the operations performed at (b) (4) facility are provided in section **3.2.P Buffer Drug Product Manufacturing- Effervescent Granule** of this memo.

IV. Facilities and Inspections

The facilities involved in the manufacture and release testing are listed in Table 1: Manufacturing facilities for DS, DP and Buffer and Table 2 : Release Testing for DS, DP and Buffer (see Table 1 and Table 2 in APPENDIX) and provide a short description of their manufacturing responsibilities and a proposal for the need for an inspection or waiver for each facility. Based on the information in the table, the following facilities are noted to either require an inspection or a waiver for inspection:

Facilities that require an Inspection:

- **PaxVax, Inc**.
  (b) (4)
- (b) (4)

Facilities to waive inspection:

- (b) (4)

(b) (4)

Please note all facilities list above will be included in the compliance check. Waiver memos were prepared for (b) (4) . After supervisory approval, waiver memos will be uploaded to EDR for reference.

V. Facilities and Equipment - The firm provided the following facility and equipment information for all facilities involved in the manufacture of DS, DP and the Buffer DP.

3.2.A.1 Facilities and Equipment for (b) (4)
PaxVax contracts out to (b) (4) , to perform the upstream fermentation and lyophilization activities in manufacture of the Intermediate Bulk Drug Substance. In section 3.2.A.1 of 3.2.A Appendices of the BLA, a site master file for (b) (4) , in addition to Report VPR-109, "PXVX0200 Validation Project Report for the Commissioning, Qualification, and Cleaning and Sanitization Validation of the Upstream Facilities, Utilities and Equipment was provided. The site master file includes details of the overall operations of (b) (4) , including information about the firm as a contract manufacturer (history, types of products manufactured, and other manufacturing activities performed), in addition to overall general details of the quality systems, production and manufacturing, validation, maintenance, equipment, cleaning, sanitization, documentation and facilities (HVAC system, water systems etc.), etc. The VPR-109 is a high level report that provides references to the individual qualification reports for process equipment, facilities and utilities and denotes the procedures, SOPs and protocols followed in maintaining the facility, utilities and equipment in a validated state. The information provided in these documents is summarized below.

General Description of Facilities (b) (4)
. PXVX0200 is manufactured in the controlled, classified space on the (b) (4)
space and associated non-clean utility and support systems).

Facilities used for manufacture of PXVX0200 include an (b) (4)

10 pages have been determined to be not releasable: b4,b5,b7e

(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

(b) (4)

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3.2.A.1 Facilities and Equipment for PaxVax, Inc. (b) (4)
Section 3.2.A.1 of 3.2.A Appendices of the BLA provides details of the facility and controls for the PaxVax, Inc.

General Description of Facilities- The PaxVax, Inc. facility is responsible for the downstream BDS manufacturing process which involves the operations of milling, blending/mixing, and filling into the primary container closure system (foil sachet) to make final DP. Pax Vax, Inc facility is also responsible for performing the filling of bulk buffer DP into foil sachets, similar operation as to the vaccine powder. The PaxVax manufacturing facility is a dedicated facility to the manufacturing of vaccine and buffer production. The facility consists of (b) (4) of classified controlled and unclassified controlled manufacturing space with the remaining space allocated for labs, offices, storage and utilities. The following was described in regards to these areas:

Classified area consists of:

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

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(b) (4)

- (b) (4)

(b) (4), (b) (5), (b) (7)(E)

Secondary Packaging Facility- Pax Vax contracts (b) (4)) to perform the secondary packaging operations for the Vaccine and Buffer. The (b) (4) site master file (provided in Section 3.2.A.1 Facilities and Equipment (b) (4) was provided which details an overview of the firm's manufacturing activities (storage and shipment, (b) (4) and dispense, primary and secondary packaging, analytical testing, inspection and stability testing), Quality policy and Quality Control system, personnel, equipment and facility systems (facility layout, building monitoring system, facility security and access, maintenance program, validation programs and cleaning), production systems (handling of materials, process validation, cleaning validation), documentation, and information in regards to distribution, customer complaints and product recall.

Reviewer Comments: (b) (4), (b) (5), (b) (7)(E)

3.2.A.1 Facilities and Equipment for (b) (4)

PaxVax contracts out the manufacture of the bulk buffer drug product to (b) (4) . In section 3.2.A.1 of 3.2.A Appendices of the BLA, a site master file for (b) (4) "Site Master File" OD0014.00 was provided. This site master file outlines

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(b) (4)

(b) (4)

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(b) (4)

(b) (4)

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VI. **3.2.S. Drug Substance Manufacturing**

3.2.S.2 Manufacture- The initial drug substance manufacturing is performed at (b) (4) which manufactures the Intermediate Bulk Drug Substance (IBDS) that is then shipped to PaxVax, Inc. for further manufacturing to Bulk Drug Substance (BDS) for intermediate storage before manufacturing to final DP (including formulation filling and labeling, operations.

(b) (4)

13 pages have been determined to be not releasable: b4,b5,b7e

(b) (4)

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(b) (4)

(b) (4), (b) (5), (b) (7)(E)

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VII. 3.2.P. Drug Product Manufacturing- PXVX0200 Powder for Oral Suspension

3.2.P.3 Manufacture

Description of Manufacturing Process Steps of Drug Product

- **Filling of the DP into sachets** (primary packaging)- After blending BDS with lactose to form the Bulk Drug Product, the bulk drug product is immediately filled into foil sachets using an automated filling machine. The filled foil sachets are heat sealed and individually weighed and measured using an automated weight checker. The accepted sachet are considered final Drug Product in primary packaging. Sachets are sampled for testing and inspection. The lot is transferred to frozen storage and drug product is test for release in comparison to approved drug product specifications.
- **Drug Product Storage**- Drug Product sachets are placed into frozen storage for long term storage until released and transported to the secondary packing CMO (b) (4)

Control of Critical Steps for DP- The classification of parameters as critical or non-critical was made by assessing the impact of each parameter from the BDS stabilization hold through drug product manufacturing and storage. Details of assessment and impact of the parameters are provided in Protocol VP-152, "PXVX0200 Cholera Vaccine Downstream Process Quality Risk

Assessment Validation" and Protocol VP-151, "Vaccine Process Definition Validation Protocol" provided in the submission. Three primary unit operations were assessed and include the following with critical parameters noted:

- BDS Stabilization hold under controlled conditions for a defined duration: (b) (4)
- Blending of BDS with dried lactose excipient at defined blending speed and duration to form BDP: (b) (4)
- Filling of BDP into filled sachets using an automated filling and packaging machine- Critical process parameters include (b) (4)

Process Validation Summary Report VP-159, PXVX0200 Cholera Vaccine Process Validation Project Plan (Downstream Manufacturing) summarizes the identification and confirmation of critical process parameters in the downstream manufacturing process as they relate to the critical quality attributes of the Cholera vaccine. These downstream production steps include: Intermediate Bulk Drug Substance (IBDS) receiving and storage, IBDS material milling and mixing processes, BDS material blending process and BDS material filling and primary packaging process and drug product storage. A summary of process parameter data and in-process testing results for each unit operation of the downstream process steps for (b) (4) commercial scale lots of BDS (lots (b) (4) is provided in Report VPR-169, "Final Report to Process Validation of Capability and Consistency for Bulk Drug Product Blend Uniformity and Drug Product Filling for the PXVX0200 Manufacturing Process" and is summarized as follows:

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug Product Release Testing

Test Method	Acceptance Criteria	Procedure	P703-1FA03 Results	P703-3FA03 Results	P703-5FA03 Results
Viable Cell Count	5 x 10^8 to 2 x 10^9 CFU/dose	Q208	2 x 10^9 CFU/dose	1 x 10^9 CFU/dose	1 x 10^9 CFU/dose
(b) (4)	(b) (4)	0493	(b) (4)	(b) (4)	(b) (4)
Absence of Specified Organisms	No growth for (b) (4)	0493	No growth for (b) (4)	No growth for (b) (4)	No growth for (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Test Method	Acceptance Criteria	Procedure	P703-1FA03 Results	P703-3FA03 Results	P703-5FA03 Results
Visual Control	Off-white sachet, two visible black marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4 sides and lot number and date of manufacture printed on the sachets is accurate and legible.	Q198	Off-white sachet, two visible black marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4 sides and lot number and date of manufacture printed on the sachets is accurate and legible.	Off-white sachet, two visible black marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4sides and lot number and date of manufacture printed on the sachets is accurate and legible.	Off-white sachet, two visible black marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4sides and lot number and date of manufacture printed on the sachets is accurate and legible.
General Safety Test	Meets 21CFR610.11	509888	Meets 21CFR610.11	Meets 21CFR610.11	Meets 21CFR610.11
Moisture content	(b) (4)	Q193 (b) (4) >	(b) (4)	(b) (4)	(b) (4)
Appearance	White to beige powder, no visible foreign particulates	Q108	Beige powder, no visible foreign particulates	White powder, no visible foreign particulates	Beige powder, no visible foreign particulates
Sachet Integrity Test	Inspection Level II with AQL of (b) (4); Failures have defect of (b) (4)	Q211	Number of allowable failures for (b) (4) samples: (b) Number of failures found: 0	Number of allowable failures for (b) (4) samples: (b) Number of failures found: 0	Number of allowable failures for (b) (4) samples: (b) Number of failures found: 0
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall Results- All lots met the acceptance criteria for all controlled/monitored parameters and for in-process testing. There were multiple deviations noted for manufacturing steps involving blending step and deviations noted during filling. Deviations associated with BDP lots were noted and involved issues with batch records in which procedures were not followed in regards to rounding off and significant figures in the batch records (DEV007). Deviations associated with DP lots involved the following deviations during filling:

DEV-008: During production, a hole in vacuum tubing to the filler was observed. Operators observed sachets not having continuous seals and upon inspection a buildup of powder on sachet sealing heads of the filler was observed. The tubing was sealed with tape and operators culled

and rejected 117 sachets that did not meet requirements for continuous seals. The root cause was identified as insufficient instruction in operating procedure for inspecting tubing for stress points that may develop holes. CAPAs were initiated to address this deviation.

UDO-15-0023: The (b) (4) package integrity testing unit was not available to perform in-process sachet integrity testing during processing under batch records P703.550.1FA03, P703.550.3FA03, and P703.550.5FA03. The root cause of the deviation was a malfunction in the (b) (4) unit. The integrity tester was subsequently repaired, re-qualified and the sachets from the lot were successfully tested. No adverse impact to the lot was identified.

PDO- 15-0018: Prior to production of drug product lots, it was observed that (b) (4) storage room (b) (4) (PV1735) was not working properly (capture in incident report INC-15-0022). Planned deviation PDO-15-0018 was initiated to document temporary storag03-1FA03, P703-3FA03, and P703-5FA03 at Pax Vax's contract clinical distribution company (b) (4). The material was transferred under temperature control to a qualified (b) (4) . Following completion of repairs and requalification of the (b) (4) room, the material was returned to Pax Vax.

UDO-15-0024: During set up (b) (4) printer, lot number P703.550-3FA03 was mistakenly entered into the system and subsequently printed on all sachets of the lot, instead of the expected P703-3FA03. Upon evaluation it was determined that the printed lot number was equivalent and there was no adverse impact to the lot.

UDO-15-0027: This deviation is associated with several issues that occurred during the filling process resulting in material losses and stoppages of the filler equipment.

1. Overflow sensor controlling the main feed auger to hopper did not properly stop flow of powder causing an overflow of powder from the sides of the product hopper. This resulted in 30% less of BDP powder. Immediate corrective action included cleaning sensor, clean the overflowed powder and monitor level in the hopper for remainder of lot. Preventative action included evaluation of design of an (b) (4) to prevent an overflow.
2. Multiple small parts to each filling auger assembly (b) (4) during each filling run. Two specific parts to the filling auger (the nut tube and washer) loosened and disengaged twice during the run. The parts were re-installed and tightened each time and the lot resumed. The impact of this would be inconsistent (b) (4) , but since the system checks the (b) (4) of each sachet produced, no adverse affected was anticipated. Root cause of this issue was identified as wear on small parts causing them to loosen over use. A preventative action was identified to evaluate the design and production of a single piece to replace the assembled auger.
3. A third issue was identified during filling, but did not result in loss of material, only stoppage during filler operation. The foil used for creation of the sachet includes registration marks at the edged, which are utilized by a laser on the filler to identify where the system should align and cut when producing sachets. A red stripe is encountered periodically on the roll of foil, which is a remnant of the foil lamination process, where two separate rolls of foil are sliced together. During production, the filler paused when the red stripe was observed, so the operator could manually remove the section with the red splice mark. If the red stripe passes in the filler, the laser can mistake this red stripe as a registration mark for alignment of the sachet for cutting causing a jam. As a preventative action, an evaluation of programming the filler to skip through this section of the foil.

Reviewer Comments: (b) (4), (b) (5), (b) (7)(E) .

(b) (4), (b) (5), (b) (7)(E)

3.2.P.7- Container Closure for DP and Buffer DP- Drug product is filled into sachets (60 mm x 90 mm) made from three-ply multilayer foil (b) (4) The sachet is heat-sealed on all four sides such that the heat seal has minimum width of (b) (4) from the inner weld line to the outer edge. Each vaccine sachet contains a single-dose (b) (4) of vaccine drug product. The materials of construction for each layer of the three layer foil sachet and their corresponding functions and manufacturer's specification are listed in the following table:

(b) (4)

(b) (4)

A type III Drug Master File (DMP (b) (4)) has been filed by (b) (4) for the foil sachets. The following was also indicated in regards to the foil sachet:

- Sealant film that comes into contact with the drug product complies with 21 CFR 174.5, 175.300, 177.1520(c)2.1, 178.2010, 178. Monomers and additives used for this sealant are listed in (EU) 10/2011 and subsequent revisions
- Sachet complies with recommendations for content of heavy metals Pb, Hg, Cd and Cr(VI)
- No Class II or Class II solvents are used to manufacture the products of the container closure system
- Foil contains no animal-derived components except for a (b) (4)

The following Specifications for the PXVX0200 Container Closure Sachet Foil was provided as follows:

Test Description	Method	Acceptance Criteria
Review of Manufacturer's Certificate of Analysis	PaxVax Q183	Results comply to vendor specifications
Visual Inspection	PaxVax Q179	Paper surface has a matte finish

Width	PaxVax Q179	(b) (4)
Identification by (b) (4)	(b) (4)	Conforms to (b) (4)

Secondary Packaging- Secondary packaging is indicated as a carton in which contents include one vaccine powder sachet, one buffer sachet and a package insert. The secondary packaging serves to protect the sachets from incurring minor cosmetic defects, such as wrinkling and folding. Additionally, the carton allows for streamlined pharmacy operations and helps reduce potential for dispensing errors. Secondary packing is a manual process that is performed at (b) (4). A facility schematic and material flow schematic was provided in the Site Master File of (b) (4). The packaging operation is controlled by a master batch record and a process validation protocol will be executed during packaging of the first commercial lot.

Container Closure Integrity Testing and Results- The CCIT methods were described by SOP Q211.02, "Sachet Integrity Test" provided in Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls of the submission. The results of CCIT were provided in VPR-169. The SOP Q211.02, "Sachet Integrity Test" was provided in the submission. The CCIT method is a non-destructive test used to detect leaks and weak seals in sachets using the (b) (4) .

Reviewer Comments: The (b) (4) *OQ/PQ was not provided in the submission* (b) (4), (b) (5), (b) (7)(E)

VIII. 3.2.P Buffer Drug Product Manufacturing- Effervescent Granule

3.2.P.3 Manufacture

Description of the Manufacturing process of Bulk Buffer Powder performed at (b) (4) The manufacturing process of the bulk buffer powder is performed at (b) (4) in an unclassified room that is environmentally monitored using class (b) (4) limits. The room temperature and relative humidity is maintained and set at (b) (4) with a relative humidity of (b) (4) The units of operations for the bulk buffer powder include the following:

- (b) (4)

(b) (4)

- **Storage and Shipping**- The bulk buffer drug product is stored at (b) (4) until release and required for shipment.

Description of the Manufacturing process of Bulk Buffer Drug Product performed at Pax Vax (Filling and Packaging)- The following steps included:

- **Filling of the Bulk Buffer Drug product DP into sachets** (primary packaging)- The bulk buffer drug product received from (b) (4) is filled into foil sachets using an automated filling machine. The filled foil sachets are heat sealed and individually (b) (4). The accepted sachet are considered final Buffer Drug Product in primary packaging. Sachets are sampled for testing and inspection. The lot is transferred to (b) (4) storage and buffer drug product is test for release in comparison to approved specifications.
- **Drug Product Storage**- Buffer rug Product sachets are placed into (b) (4) storage for long term storage until release and transported to the secondary packing CMO (b) (4)

3.2.P.4 Control of Critical Steps and Intermediates

Control of Critical Steps for Blending of Bulk Buffer Drug Product (buffer)- The following critical parameters were indicated for the blending of the bulk buffer drug product, performed at (b) (4)
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Control of Critical Steps for Filling and Primary Packaging- The following critical parameters were indicated for the filling (in foil sachets) and primary packaging of the Bulk Buffer Drug Product:

- (b) (4)

(b) (4)

3.2.P.7- Container Closure for Buffer in later section of memo.

- (b) (4)

3.2.P.5 Process Validation and/or Evaluation [Buffer, Effervescent Granule]

Process Validation Summary of Bulk Buffer Drug Product Filling-The results of three commercial scale lots of Buffer Drug Product were provided in Report VPR-177 to support the capability and consistency of the filling of the bulk buffer drug product into the primary packaging. The report is summarized as follows:

Listing of Commercial Scale Validation Lots manufactured in validation:

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.7- Container Closure for Buffer - Buffer is filled into sachets (60 mm x 90 mm) made from three-ply multilayer foil (b) (4) identical to the sachets used for the vaccine drug product. The sachet is heat-sealed on all four sides such that the heat-seal has a minimum of width of (b) (4) from the inner weld line to the outer edge. Each sachet contains a single dose of buffer. The material specifications and references to the Type III Drug Master File of the foil material that is used to make the foil sachets are the same as the information previously reviewed for the container closure of the vaccine powder drug product. For details, please refer to the 3.2.P.7 Container Closure for DP in previous section of this memo. Additionally, this section also includes the details of the secondary packaging and the CCIT methods used to test integrity of the sachet primary package.

IX. **Environmental Assessment**-The firm has provided an Environmental Analysis in section 1.12.14 of the BLA. Thus, the firm is not requesting a categorical exclusion. The review and adequacy of the Environmental Analysis is out of the scope of this review and requires the expertise of the product office, thus the review of this documentation is deferred to the product office.

X. Information Requests- During this primary review, the following information requests were sent to the firm. The firm's responses will be covered in the addendum review memo.

IR#1 sent 1/13/16- Firm was asked to respond no later than February 12, 2016

1. For the equipment used in the upstream manufacturing operations at (b) (4), please provide a listing of all major product contact equipment used in the manufacturing of the intermediate bulk drug substance and indicate if the equipment is shared or dedicated and how this equipment is cleaned (i.e. CIP or manual) and/or sterilized (if applicable).
2. Please provide the summaries of the qualifications (OQ and PQ) for the HVAC system, in addition to major equipment (fermenters, freezer dryer, and BSCs) used in the manufacturing of intermediate bulk drug substance at (b) (4).
3. Please provide the cleaning validations for major product contact equipment (fermenters, freezer dryer etc.) used at (b) (4) for the manufacturing of intermediate bulk drug substance.

IR#2 sent 3/1/16- No time frame for response was indicated

1. Please provide a summary report of "deviation 01" noted in footnote of Tables 5 (pg.15) and 9 (pg.25) provided in VPR-154, "Interim Report for the cleaning validation for PaxVax Building (b)(Process Equipment". This summary should include details for the exclusion of the (b) (4) and (b) (4) from the cleaning load during the process validation.

IR#3 sent 3/11/16- Firm was asked to respond by March 24, 2016.

1. In regards to the acceptance criteria for the cleaning validation of the equipment used for manufacturing of the Bulk Drug Substance (BDS) and Drug Product (DP) (indicated in Table 1 of VPR-154), the (b) (4) [redacted] Please indicate why the (b) (4) [redacted] acceptance criteria for equipment cleaning increases with the progression of the manufacturing steps.

XI. (b) (4), (b) (5), (b) (7)(E) [redacted].

(b) (4), (b) (5), (b) (7)(E) [redacted].

(b) (4), (b) (5), (b) (7)(E) [redacted]

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APPENDIX

Table 1: Manufacturing Facilities for DS (IBDS and BDS), DP and Buffer DP

Name/Address	Responsibility	FEI & DUNS Numbers/ Inspection History	Inspection Y or N Justification
(b) (4)	Original manufacturer of Master and Working Seed Lot	NA	(b) (4)
(b) (4)	Manufacturer of Working Seed Lot	NA	(b) (4)
(b) (4)	-Manufacturer of Intermediate bulk substance (IBDS)	(b) (4)	(b) (4)
PaxVax, Inc. (b) (4)	-Manufacturer of Bulk Drug Substance (BDS) -DP Manufacturing -primary packaging of drug product -Filling and primary packaging of buffer drug substance	(b) (4)	(b) (4)
(b) (4)	-Manufacturer of bulk Buffer blend	(b) (4)	(b) (4)
(b) (4)	-Secondary packaging of DP and Buffer DP	(b) (4) (b) (4)	(b) (4)

Table 2 Release Testing facilities for DS (IBDS and BDS), DP and Buffer Drug Product

Name/Address	Responsibility	FEI & DUNS Numbers/Inspection History	Inspection Y or N with Justification
(b) (4)	Master Seed Lot and Working Seed Lot Release and Stability testing Potency by Viable cell count Release Testing Purity of (b) (4)	(b) (4)	(b) (4)
(b) (4)	Release Testing of Intermediate Drug Substance (IBDS) • (b) (4) Release Testing of Bulk Drug Substance (BDS) • (b) (4) DP release Testing • Identity by (b) (4) • Identity by (b) (4) • General Safety	(b) (4)	(b) (4)
(b) (4)	IBDS Release Testing • (b) (4)	(b) (4)	(b) (4)
(b) (4)	IBDS Release Testing • (b) (4) (b) (4) IBDS Release and Stability Testing • (b) (4) BDS Release and Stability Testing • (b) (4) DP Release and Stability Testing • (b) (4) DP Release Testing • Absence of specified organisms (b) (4)	(b) (4) (b) (4)	(b) (4)

	(b) (4)		
*PaxVax (b) (4)	IBDS Release Testing • (b) (4) IBDS Stability Testing • (b) (4) BDS Release and Stability Testing • (b) (4) • (b) (4) DP Release Testing • all release and stability testing except Identity, general safety, absence of specified organisms and (b) (4)	(b) (4) (b) (4)	(b) (4)
(b) (4)	IBDS In-Process testing (b) (4)	(b) (4)	(b) (4)

*Please note these facilities also perform some in-process testing; however, these tests are not included this table

**Additionally, please note that facilities involved with in-process testing of Master Seed Lot and Working Seed Lot are not included in this table, only facilities performing testing on IBDS, BDS, DP and buffer are included.

***This facility is only used as secondary laboratory. The primary testing is performed at (b) (4)

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(b) (4)